Pharmacokinetic and Analytical Issues in Busulfan Area Under the Curve Estimation and Simulation

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To the Editor:

We read with interest the recently published article by Zao et al. [1]. In this study they compared the performance of different guidelines for initial dosing of intravenous busulfan in children. Their results indicated that 12 identified guidelines vary in their ability to achieve the conventional therapeutic target range (900 to 1500 μM/min) of busulfan area under the concentration time curve (AUC). We have several concerns regarding the methods used in their study, and several points should be clarified for correct interpretation of their results by readers.

First, they used the AUC estimated in 111 children as the reference value for all simulations of dosing guidelines. Therefore, the precision of the AUC estimation in those 111 children is critical in this work. However, the authors provide little information on this point. Apparently, they used 2 methods to estimate the individual AUC: a 1-compartment model implemented in WinNonLin and a previously published regression equation based on limited-sampling strategy. Several points are unclear:

- Why did the author use 2 methods instead of 1?
- Which method was used for the estimation of pharmacokinetic parameters with the 1-compartment model?

Also, the number of samples per patient, the sample day, the sampling times, and the type of AUC (AUC from time 0 to 6 hours or from 0 to infinity) are unknown but are all important in the precision of AUC estimation. The performance of each method in estimating the AUC should also be provided, because a precise and unbiased estimation is required for performing subsequent simulations based on those AUC values.

Second, no information is provided about the busulfan assay method. The precision of the assay method is not provided, even though it has been shown that the between-run precision can vary by a factor of 2 (from 7% to 15% [2-7]). This can influence the AUC estimation. Moreover, no information has been provided about the storage of plasma samples. Busulfan plasma samples need to be place in an ice bath at 4°C for a 24-hour maximum delay and then stored at −20°C until the assay [4,8].

Third, Zao et al. simulated the AUC achieved with the initial dosing regimen of busulfan recommended by various guidelines. For each patient simulated busulfan AUCs were calculated using a linear relationship between dose and AUC as follows:

$$AUC_{simulated} = \frac{Dose_{proposed}}{Dose_{initial}} \times AUC_{observed}$$

where $Dose_{proposed}$ is the dose proposed by the dosing guidelines and $AUC_{observed}$ is the busulfan AUC calculated with the $Dose_{initial}$ (from their retrospective chart review) and either a 1-compartment model or a limited-sampling strategy.

There is a lack of important details on this calculation of the simulated AUC. Is it the AUC per administration (AUC_{0-6}) reached at the steady state or the mean of 16 AUC_{0-6}? It is noteworthy that this calculation is valid only if $AUC_{simulated}$ is the AUC during a dose interval at the steady state and if $AUC_{observed}$ is the AUC from time 0 to infinity after a single dose [9]. Because there is a substantial accumulation of busulfan after repeated i.v. administrations, the AUC_{0-6} observed over the first dosing interval is significantly lower than that at the steady state and should never be used in such calculation.

The objective of the study from Zao et al. was valuable and clinically relevant. It is likely that the author's conclusion that AUC target attainment rates substantially vary between the various dosing guidelines of busulfan is correct. However, important details on the pharmacokinetic calculations performed with both the real and simulated dataset are lacking, and this make the validity of the results uncertain.

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